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ABSTRACT

Renal phosphate handling critically determines plasma phosphate and whole body phosphate levels. Filtered phosphate is mostly reabsorbed by Na^+-dependent phosphate transporters located in the brush border membrane of the proximal tubule: NaPi-IIa (SLC34A1), NaPi-IIc (SLC34A3), and Pit-2 (SLC20A2). Here we review new evidence for the role and relevance of these transporters in inherited disorders of renal phosphate handling. The importance of NaPi-IIa and NaPi-IIc for renal phosphate reabsorption and mineral homeostasis has been highlighted by the identification of mutations in these transporters in a subset of patients with infantile idiopathic hypercalcemia (IIH) and patients with Hereditary Hypophosphatemic Rickets with Hypercalciuria (HHRH). Both diseases are characterized by disturbed calcium homeostasis secondary to elevated 1,25-$(OH)_2$ vitamin D_3 as a consequence of hypophosphatemia. In vitro analysis of mutated NaPi-IIa or NaPi-IIc transporters suggests defective trafficking underlying disease in most cases. Monoallelic pathogenic mutations in both SLC34A1 and SLC34A3 appear to be very frequent in the general population and have been associated with kidney stones. Consistent with these findings, genome-wide association studies indicate that variants in SLC34A1 are associated with a higher risk to develop kidney stones and chronic kidney disease but underlying mechanisms have not been addressed to date.

Systemic phosphate balance depends on renal excretion

Phosphate is the third most abundant anion in the human body and accounts for about 1% of total body mass. Approximately 80-85 % of total phosphate content is stored in bone in the form of apatite, contributing to bone stability, about 15 % is distributed in soft tissues, and only 1 % is contained in the rapidly exchangeable plasma pool.

Phosphate balance depends on dietary intake and intestinal absorption, distribution between organs, and renal filtration and reabsorption. As discussed below, it is mainly renal handling that is tightly regulated and thereby exerts ultimate control over whole body phosphate homeostasis. The recommended daily allowance (RDA) for phosphate is age-dependent. Infants are recommended to receive daily about 100-275 mg and children and adolescents 460-1250 mg/day [1]. In growing children phosphate balance should be positive to support building of bone and growth of soft tissues. In adults, intestinal net absorption and renal net excretion should ultimately remain zero to avoid phosphate overload or deficiency, respectively. However, in most industrialized countries phosphate content of food exceeds RDA [2-4].

The mechanisms underlying intestinal phosphate absorption are not fully elucidated. At present, experimental evidence from humans and animal models supports a bimodal pathway consisting of a transcellular, transporter-dependent pathway and a poorly defined paracellular route [5]. The transcellular route involves the sodium-driven phosphate transporter NaPi-IIb (Npt2b, SLC34A2) mostly expressed in the jejunum in humans [6-7]. The expression of the transporter is regulated by dietary phosphate intake and 1,25 $(OH)_2$ vitamin D_3 [8-10]. However, the overall contribution of this transporter to intestinal phosphate absorption may be low, at least under normal phosphate intake, as evident from mouse models deficient for NaPi-IIb/Slc34a2 and from humans with the rare inborn condition of pulmonary alveolar microlithiasis caused by loss-of-function mutations in SLC34A2/NaPi-IIb [8, 11-12]. NaPi-IIb depleted mice do not suffer from hypophosphatemia or any other obvious sign of systemic phosphate deficiency unless challenged with a low phosphate diet [8, 13-14]. During low Pi availability, NaPi-IIb deficient mice become highly hypercalciuric, at least in part due to increased osteoclast activity providing phosphate to the organism at the expense of bone density [14]. In humans with

SLC34A2 mutations, no detailed analysis of phosphate balance has been reported to date. Two other phosphate transporters, PiT1 (SLC20A1) and PiT2 (SLC20A2) are also expressed in the small and large intestine at rather low levels and their role and contribution to intestinal phosphate absorption are unknown. Patients with mutations in SLC20A2 develop basal ganglia calcifications but no other symptoms relating to systemic phosphate homeostasis have been reported [15].

Renal phosphate transporters

Renal phosphate excretion depends on the filtered load of phosphate and its subsequent reabsorption along the nephron. There is no evidence for active secretion of phosphate into urine. The bulk of tubular phosphate reabsorption occurs in the proximal tubule with some evidence pointing also to a smaller component of active reabsorption in segments between the late proximal tubule and the connecting tubule [16].

In the proximal tubule, at least three different sodium-driven phosphate transporters mediate the initial step of phosphate reabsorption across the apical brush border membrane: NaPi-IIa (Npt2a, SLC34A1), NaPi-IIc (Npt2c, SLC34A3), and PiT2 (SLC20A2) (Figure 1) [17-18]. As discussed below, all evidence suggests that NaPi-IIa and NaPi-IIc play important roles in humans and rodent models but possibly to different extent. The basolateral exit pathway for phosphate remains unknown but may involve a mechanism of anion exchange [19-20]. Also, the molecular identity of potential phosphate transporter(s) in the more distal nephron segments has not been reported.

The three phosphate transporters expressed in the proximal tubule exhibit different transport modes, sensitivity to pH, and dynamics of regulation by dietary phosphate intake and phosphaturic hormones. Briefly, NaPi-IIa and NaPi-IIc transport divalent phosphate (HPO_4^{2-}) whereas PiT2 prefers monovalent phosphate ($H_2PO_4^-$). Moreover, NaPi-IIa and PiT2 mediate electrogenic transport of phosphate because of their coupling of the transport cycle to 3 or 2 Na^+ ions, respectively, leading to the net translocation of one positive charge per phosphate ion. NaPi-IIc transports only 2 Na^+ ions per phosphate and is therefore electroneutral (Figure 1). Domains in NaPi-IIa and NaPi-IIc involved in sodium and phosphate binding have been identified [21].

Because of their different sensitivity to extracellular protons and preferred phosphate species (di- vs monovalent phosphate), NaPi-IIa and NaPi-IIc operate most efficiently at a near neutral pH (~ pH 7.4 – 7.0) whereas PiT2 would become more active at slightly more acidic conditions [18, 22].

Inherited forms of renal phosphate wasting

Renal phosphate wasting can occur as part of several systemic syndromes, generalized inherited or acquired dysfunction of the proximal tubule (e.g. Debre-DeToni-Fanconi syndrome) and in a number of inherited disorders specifically affecting renal and extrarenal phosphate homeostasis (for review see [23-24]). Most inherited extrarenal disorders leading to changes in renal phosphate handling are caused by mutations in FGF23 or factors controlling FGF23 levels or sensitivity of target cells. Thus, disorders like X-linked hypophosphatemia (XLH; *PHEX* mutations), autosomal dominant hypophosphatemic rickets (ADHR; *FGF23* mutations), familial tumoral calcinosis (FTC; *GALNT3* or *FGF23* mutations), fibrous dysplasia (McCune-Albright syndrome; *GNAS* mutations), osteoglophonic dysplasia (FGF-receptor 1 (*FGFR1*) mutations), osteosclerotic bone dysplasia (Raine syndrome; *FAM20c*), or autosomal recessive hypophosphatemic rickets (ARHR; *DMP1* or *ENPP1* mutations), also known as autosomal recessive hypophosphatemia (ARHP), are primarily extrarenal disorders affecting renal phosphate handling [23-26].

In contrast, mutations in NaPi-IIa, NaPi-IIc and maybe also in NHERF1 (Na/H exchanger factor 1) directly affect the renal capacity to reabsorb phosphate. The roles of two other proteins potentially involved in renal phosphate handling, PiT2 and XPR1, are currently unclear even though mutations in both genes have been described in patients. .

Mutations in SLC34A1 and SLC34A3 cause nephrocalcinosis and kidney stones. The pathogenesis of nephrocalcinosis in the setting of various inherited and acquired kidney diseases has recently been reviewed in much detail [27-30]. The pathophysiology underlying nephrocalcinosis in patients with SLC34A1 and SLC34A3 is thought to be caused by the primary loss of phosphate with urine, the consecutive stimulation of 1,25 $(OH)_2$ vitamin D_3 synthesis leading to enhanced intestinal calcium absorption and calcium overload. Renal excretion of calcium

causes hypercalciuria which together with elevated urinary phosphate levels can trigger the formation of calcium-phosphate containing crystals favoring the development of renal calcifications.

NaPi-IIa (*SLC34A1)*

SLC34A1 has been linked to phosphate homeostasis in humans by several lines of evidence. A genome wide association study (GWAS) for determinants of serum phosphate levels identified *SLC34A1* among other genes including *FGF23* and the Calcium-sensing receptor *CaSR* [31]. Similarly, GWAS for nephrolithiasis in a sample of an adult Japanese population linked to a region near 5q35.3, implicating *SLC34A1* (located at this site) in calcium phosphate kidney stone disease [32-34]. Also the Icelandic genome analysis consortium identified *SLC34A1* next to the *CaSR* and alkaline phosphatase as a risk gene for kidney stones and identified one specific marker within *SLC34A1* as being associated with hypophosphatemia and low PTH [35].

Homozygous and (compound) heterozygous mutations, or small insertions and deletions in *SLC34A1* were independently identified by several laboratories when investigating adult patients with kidney stones and reduced bone density [36] or pediatric patients with either hypophosphatemia and hyperphosphaturia [37], infantile idiopathic hypercalciuria [38], or with nephrocalcinosis and kidney stones [35, 39-44]. Larger deletions including the *SLC34A1* gene can occur as part of Sotos syndrome characterized by learning deficiencies, facial dysmorphia, overgrowth, hypercalcemia, and nephrocalcinosis [45].

Up to date, 29 distinct mutations have been identified in *SLC34A1*, mostly causing missense mutations, small in-frame deletions, frame shifts or early stop-codons resulting in a truncated transporter (Figure 2A, Supplementary Table 1) [35-37, 39-42, 44, 46]. Interestingly, most of these mutations appear to be located within regions predicted to be part of the transmembrane domains of the transporter. These regions are often highly conserved in transport proteins and are more sensitive to changes in their structure. Several of these mutated proteins were expressed and functionally analyzed in heterologous expression systems such as Xenopus oocytes or the opossum kidney (OK) cell line resembling the proximal tubule. Collectively, these studies show reduced function of mutated transporters mostly due to trafficking

defects, with mutant proteins retained intracellularly [37-38, 41]. However, one mutation is of particular interest: a small in-frame deletion of 7 amino acids at the N-terminus of NaPi-IIa (91del7) was identified in several patients as either one of two mutated alleles (compound heterozygous patients) or as homozygous mutation in at least one patient [38]. All these patients show symptoms similar to patients with other pathogenic mutations suggesting that this mutation is deleterious. However, in vitro analysis in Xenopus oocytes shows no obvious transport defect [38, 47] whereas expression of the mutant protein in OK cells suggested reduced apical expression and partial retention, pointing to a possible trafficking defect [38]. Interestingly, inspection of public data bases like ExAC shows a high allele frequency of 0.018 suggesting that approximately 2 % of the general population are heterozygous carriers of this mutation. The combined allele frequency of all proven pathogenic exonic mutations is 0.022 whereas the total allele frequency of all nucleotide changes leading to an altered amino acid sequence sums up to 0.07. The relevance of this finding is currently unclear but may link to an increased risk of developing calcium phosphate kidney stones in adulthood.

In pediatric patients, *SLC34A1* mutations were mostly homozygous or compound heterozygous and the pattern of inheritance was autosomal recessive. No obvious pathology was detected in parents or other family members carrying only one affected allele. In contrast, three adult patients were described with only one allele mutated and presenting with calcium phosphate stones and reduced bone density [36]. However, no further genetic information was available and considering the relatively high frequency of stone disease and its association with reduced bone density in the adult population, it remains unclear whether the symptoms in these patients were caused by *SLC34A1* mutations. Moreover, detailed functional analysis of the two reported gene variants yielded no obvious defect [48]. Also, in other families of affected homozygous patients, heterozygous carriers did not present with a high frequency of kidney stones suggesting that heterozygosity *per se* may not cause a higher risk for kidney stones [37]. However, GWAS clearly support a role of *SLC34A1* in stone disease [32-33, 35]. NaPi-IIa interacts with itself by forming homodimers of two transporters [49]. Both subunits function independently in the healthy state [50]. It is unknown at which cellular level the interaction occurs (e.g. at the level of the endoplasmic reticulum, Golgi or plasma membrane) and whether interaction of a normal transporter with a mutant transporter may accelerate

degradation or reduce membrane insertion. Interactions between normal and mutant transporter could reduce overall expression of NaPi-IIa by up to 75 % and thereby help explaining some of the clinical observations made in heterozygous carriers of NaPi-IIa mutations. Thus, it remains to be examined whether additional genetic or environmental factors together with the presence of one mutated allele may cause a higher risk for kidney stone disease.

Indeed, a mouse model of *Slc34a1* deficiency presents calcium phosphate and calcium oxalate containing renal calcifications when challenged with high phosphate or oxalatediets [51-52]. Slc34a1 KO mice like human patients with *SLC34A1* mutations are hypercalciuric [38, 53]. The renal loss of phosphate stimulates activation of 1,25$(OH)_2$ vitamin D_3 by the renal 1-alpha-hydroxylase (CYP27B1) and reduces inactivation by the 24-hydroxylase (CYP24A1). The elevated levels of 1,25$(OH)_2$ vitamin D_3 stimulate intestinal phosphate and calcium absorption. The latter is excreted by the kidney causing hypercalcuria and an increased risk of nephrolithiasis and –calcinosis. Consistently, restricted 1,25$(OH)_2$ vitamin D_3 synthesis (or lower vitamin D_3 supply) and enhanced phosphate supplementation reduces renal calcifications [54]. Thus, children with *SLC34A1* mutations likely benefit from phosphate supplements and should not receive standard vitamin D_3 supplements during the first years of life. Whether mutation of one allele is sufficient to trigger a similar mechanism is currently unknown but may depend, among other factors, on dietary supply of vitamin D_3, phosphate, and calcium.

NaPi-IIc (SLC34A3)

Mutations in *SLC34A3* are the cause of hereditary hypophosphatemic rickets with hypercalciuria (HHRH) [55-57]. In contrast to patients with mutations in *SLC34A1,* rickets is a common feature along with hypophosphatemia, hyperphosphaturia, hypercalciuria, and elevated 1,25$(OH)_2$ vitamin D_3. Consequently, many patients develop kidney stones or nephrocalcinosis. It appears that problems persist into adulthood whereas the clinical symptoms in patients with *SLC34A1* mutations may improve with reaching adulthood suggesting that NaPi-IIa may play a more prominent role in earlier phases of life and NaPi-IIc may be the more important transporter in adult kidney (in contrast to rodents where NaPiIIc

appears to be mostly expressed during growth). However, this is based only on few observations and longer follow-ups are required in patients with the different mutations.

Up to date, 32 different mutations in *SLC34A3* have been reported [55-70] including mostly missense mutations, mutations affecting potential splice sites, and smaller and larger deletions causing premature stop codons with expression of a truncated transporter (Figure 2B, supplementary table 2). Some of these mutations have been further characterized using in vitro expression systems and found to cause mostly retention in the endoplasmic reticulum, but also to reduce the stability in the plasma membrane, or to decrease transport activity [57-58, 62] similar to findings for *SLC34A1* mutations. Proven pathogenic *SLC34A3* mutations (allele frequency 0.002) are less frequent in the general population than for *SLC34A1*. However, when considering suspected mutations (e.g. without clear genetic or experimental proof) total allele frequency increases to 1.5 but mostly due to two very frequent allele variants with nearly 0.4 and 0.8 allele frequency. At this point, the relevance for NaPi-IIc activity is unclear and requires better genetic and experimental proof to provide insights whether these alleles may contribute to an increased risk to develop kidney stones as discussed above for *SLC34A1*.

Different mouse models of NaPi-IIc deficiency have been created to further examine the role of the transporter and to gain better insights into the pathology of HHRH. A constitutive Slc34a3 KO mouse model showed normal growth, no evidence for renal phosphate losses, was normophosphatemic and had normal bone growth and morphology [71]. However, NaPi-IIc KO mice had hypercalcemia, hypercalciuria and high levels of $1,25(OH)_2$ vitamin D_3, whereas FGF23 is reduced [71]. A second mouse model with an inducible deletion of renal NaPi-IIc was generated to examine whether acute or chronic compensatory mechanisms may mask some of the expected pathology in the constitutive KO mouse. Surprisingly, inducible NaPi-IIc KO mice showed no biochemical abnormalities and had similar levels of calcium in plasma and urine as well as normal $1,25(OH)_2$ vitamin D_3 and FGF23. No evidence for compensation by other renal phosphate transporters, i.e. NaPi-IIa or PiT2, was found [72].

NHERF1

NHERF1, also known as PDZK3 or Binding Protein 50 (EBP50), is encoded by the *SLC9A3R1* gene and acts as a scaffold protein for brush border membrane associated proteins in the proximal tubule. Among its binding partners are NaPi-IIa, the parathyroid hormone receptor 1 and phospholipase C [73-78]. NHERF1 stabilizes these proteins at the brush border membrane and creates a platform for PTH signaling to NaPi-IIa [73-74, 79-81]. Prie and colleagues reported in total 8 patients with hyperphosphaturia and kidney stone disease carrying heterozygous gene variants in NHERF1 [82-83]. Expression of the L110V, R153Q, and E225K gene variants in cell culture models increased PTH responsive downregulation of NaPi-IIa [82]. The E68A variant was reported to disrupt the interaction with NaPi-IIa possibly leading to destabilization of the transporter at the brush border membrane [83]. Of note all patients were only heterozygous carriers of the reported variants and as noted by others the same gene variants are found at high frequency in public databases, raising the question whether the observed gene variants are causative for disease [84]. Also, mice lacking only one copy of NHERF1 show no major abnormalities [78, 81].

Other renal phosphate transporters

The kidney expresses at least two further proteins that may also participate in renal phosphate transport: PiT2 (SLC20A2) and XPR1 (xenotropic and polytropic retrovirus receptor 1).

SLC20A2

The expression and localization of PiT2 has been described in some detail in rodent kidney. PiT2 localizes to the brush border membrane of the proximal tubule, colocalizing with NaPi-IIa and NaPi-IIc [85-86]. More recently, a subset of patients with familial idiopathic basal ganglia calcification, a specific form of primary brain calcifications, was shown to harbor mutations in *SLC20A2* [15, 87]. However, no renal phenotype or disorders related to phosphate homeostasis, but other defects, have been reported to date. Thus, the role of SLC20A2 in renal phosphate handling and inherited disorders of mineral balance remains to be examined.

XPR1

XPR1 has been linked to phosphate transport based on its homology to plant and yeast phosphate transporters, on harboring an SPX domain found in various plants, yeast and bacterial proteins involved in cellular phosphate homeostasis, and on the modulation of phosphate efflux from plant and mammalian cells with XPR1 deficiency or overexpression [88-89]. It has been suggested that XPR1 may be part of the long-sought basolateral efflux pathway in epithelial cells of the kidney and small intestine and/or may participate in cellular phosphate sensing [90]. Indeed, *XPR1* mRNA expression is high in kidney and small intestine in rodents. However, definite proof is lacking regarding the basolateral expression of XPR1 in kidney and intestinal epithelia, as well as its implication in the actual transport pathway and/or cellular phosphate sensor in mammalian cells. The data presented to date clearly support a role in cellular phosphate homeostasis but conclusions are mostly based on experiments from plant cells, yeast or prokaryotic systems. Interestingly, mutations in *XPR1* are also found in some patients with familial idiopathic basal ganglia calcification [91-92]. However a renal involvement has not been reported to date. A recent study with an inducible kidney-specific *Xpr1* KO mouse demonstrated a very severe disease with symptoms of a generalized proximal tubular defect, mild hypophosphatemia and bone disease [93]. However, the study did not provide definite answers to the question whether XPR1 is part of the basolateral phosphate efflux pathway.

GLUT2 (SLC2A2)

Patients from two consanginous families were reported that presented with hypophosphatemic rickets and renal phosphate wasting in the one family and with a generalized proximal tubulopathy including hypercalciuria and only mildy increased urinary phosphate excretion in the second family [94]. Genetic analysis revealed two novel homozygous mutations, IVS4-2A>G and R124S, in the SLC2A2 gene encoding the GLUT2 glucose transporter. GLUT2 is localized at the basolateral side of proximal tubule cells and serves as main exit pathway for glucose. Mutations in SLC2A2 are the cause of the Fanconi-Bickel syndrome that includes a generalized

dysfunction of proximal tubule cells with urinary loss of low molecular weight proteins, bicarbonate, glucose, and phosphate [95-96]. Of interest, mice lacking Glut2 in kidney showed greatly reduced expression levels of NaPiIIa and NaPiIIc at least in part explaining the urinary phosphate loss [94]. Thus, mutations of genes such as that affect the general function of the proximal tubule may also cause renal phosphate losses as in Dent's disease due to mutations in CLCN5 or ORCL [97-98].

Relevance of SLC34A1 for chronic kidney disease

Genome-wide association studies have linked *SLC34A1* to the risk for developing chronic kidney disease [99-100]. This association has been replicated in large cohorts with different ethnic background and shows a very high significance [101-102]. Progression of kidney disease has been shown to associate with reduced *SLC34A1* mRNA and protein expression in human kidney biopsies [103]. However, whether the reduced SLC34A1 is cause or consequence of kidney disease remains unclear. Detailed functional analysis of the genetic loci linking *SLC34A1* to CKD risk and development of suitable animal models may be needed to unravel the nature of this association. Also, the frequency of SNPs in the general population and in patients with CKD has to be examined to determine the relevance of SLC34A1 for CKD. Nevertheless, the fact that rare pathogenic mutations in SLC34A1 cause nephrocalcinosis and progressive loss of renal function, at least in some patients, may suggest that less severe alterations in SLC34A1 function may contribute to a slower loss of kidney function in adults.

Summary and outlook

The kidney is the gate-keeper of systemic phosphate homeostasis and the severe alterations in mineral homeostasis found in patients with mutations in key players of renal phosphate handling underline this notion. Biallelic mutations in the coding regions of the renal phosphate transporters *SLC34A1* (NaPi-IIa) and *SLC34A3* (NaPi-IIc) cause massive renal phosphate loss leading to secondary elevation of $1,25(OH)_2$ vitamin D_3 and hypercalciuria, driving the development of nephrolithiasis or -calcinosis predisposing to progressive loss of renal function.

Surprisingly, monoallelic pathogenic mutations in *SLC34A1* and *SLC34A3* are relatively frequent in the general population. Whether carriers of these mutations may have a higher risk for developing kidney stones remains to be fully established. Moreover, *SLC34A1* is associated with the risk for developing CKD in the general population but mechanisms and its relevance to overall CKD risk remain to be examined.

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Figure legends

Figure 1

Scheme of renal phosphate handling: **(A)** Renal phosphate reabsorption occurs mostly in the proximal segments of the nephron (orange). The segmental localization of all three known apical phosphate transporters is schematically shown in the nephron models. **(B)** Immunolocalization of NaPi-IIa, NaPi-IIc and Pit-2 in rat kidney under phosphate depleted conditions showing expression of NaPi-IIa in early and late segments of the proximal tubule whereas NaPi-IIc and Pit-2 are localized only in the early proximal tubule. High magnification of early proximal tubules with NaPi-IIa, NaPi-IIc and Pit-2 stained in green, brush border membranes are marked in red showing colocalization (yellow). Some NaPi-IIa molecules are also seen in intracellular compartments presumably in the Golgi apparatus. **(C)** Model of a proximal tubule cell, with NaPi-IIa, NaPi-IIc, and Pit-2 localized in the brush border membrane, mediating Na^+-dependent reabsorption of phosphate. Phosphate reabsorption is mostly energized by the activity of basolateral Na^+/K^+-ATPases. The basolateral exit pathway for phosphate is not well defined.

Figure 2

Predicted models of NaPi-IIa (*SLC34A1*) and NaPi-IIc (*SLC34A3*) and localization of mutations identified in patients. For details on mutations and references see supplementary tables.

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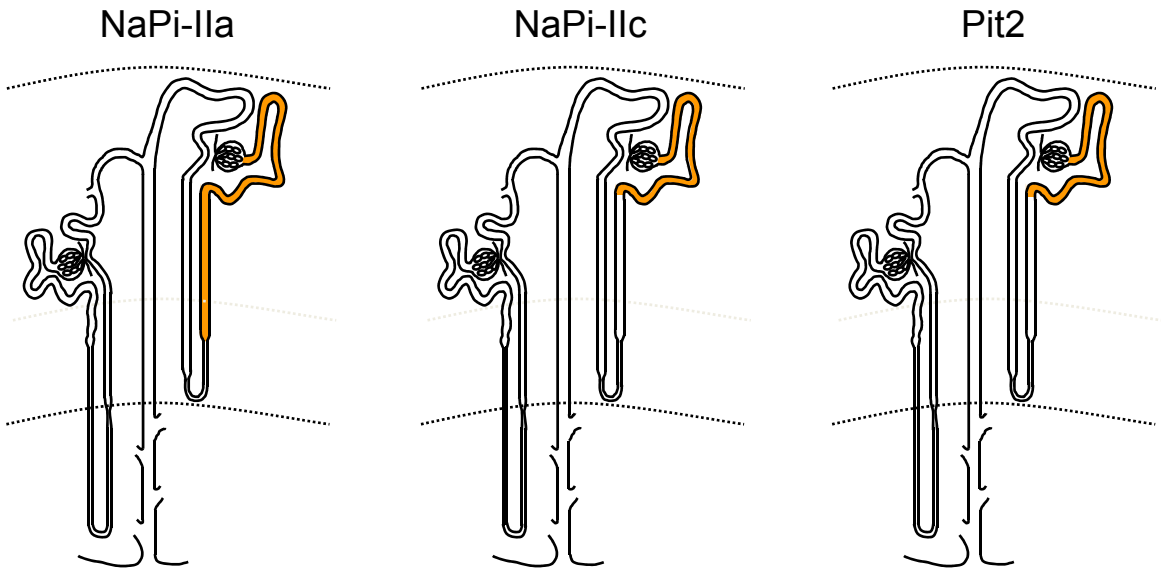
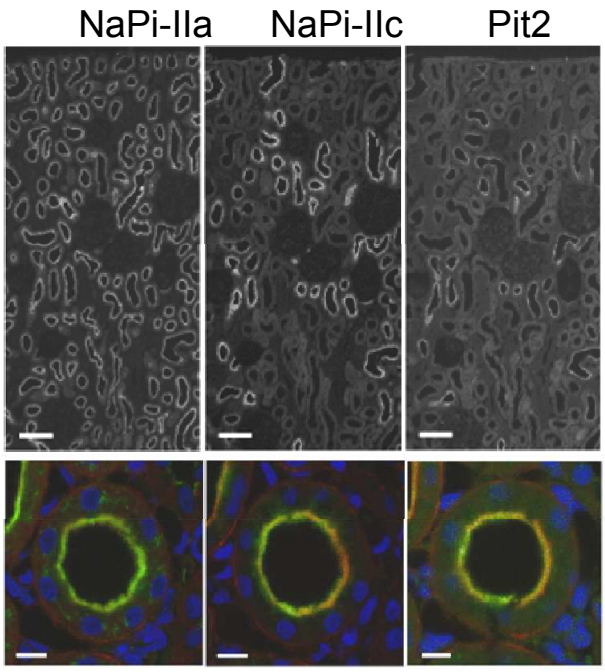
Figure 1

A


NaPi-IIa
NaPi-IIc
Pit2

B


NaPi-IIa
NaPi-IIc
Pit2

C

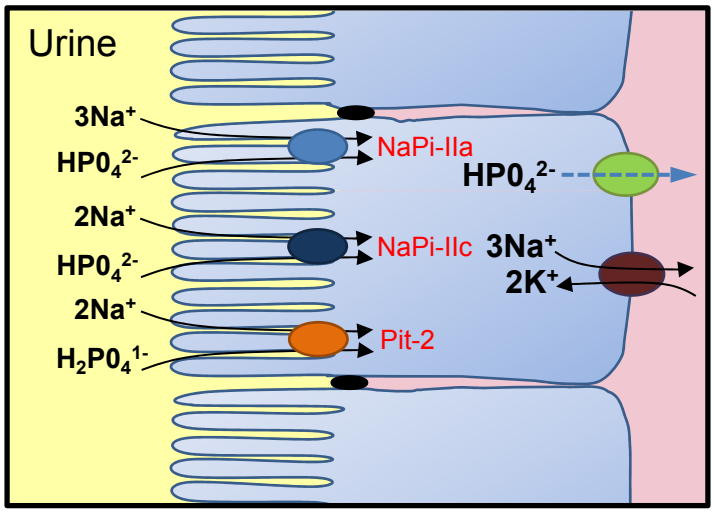
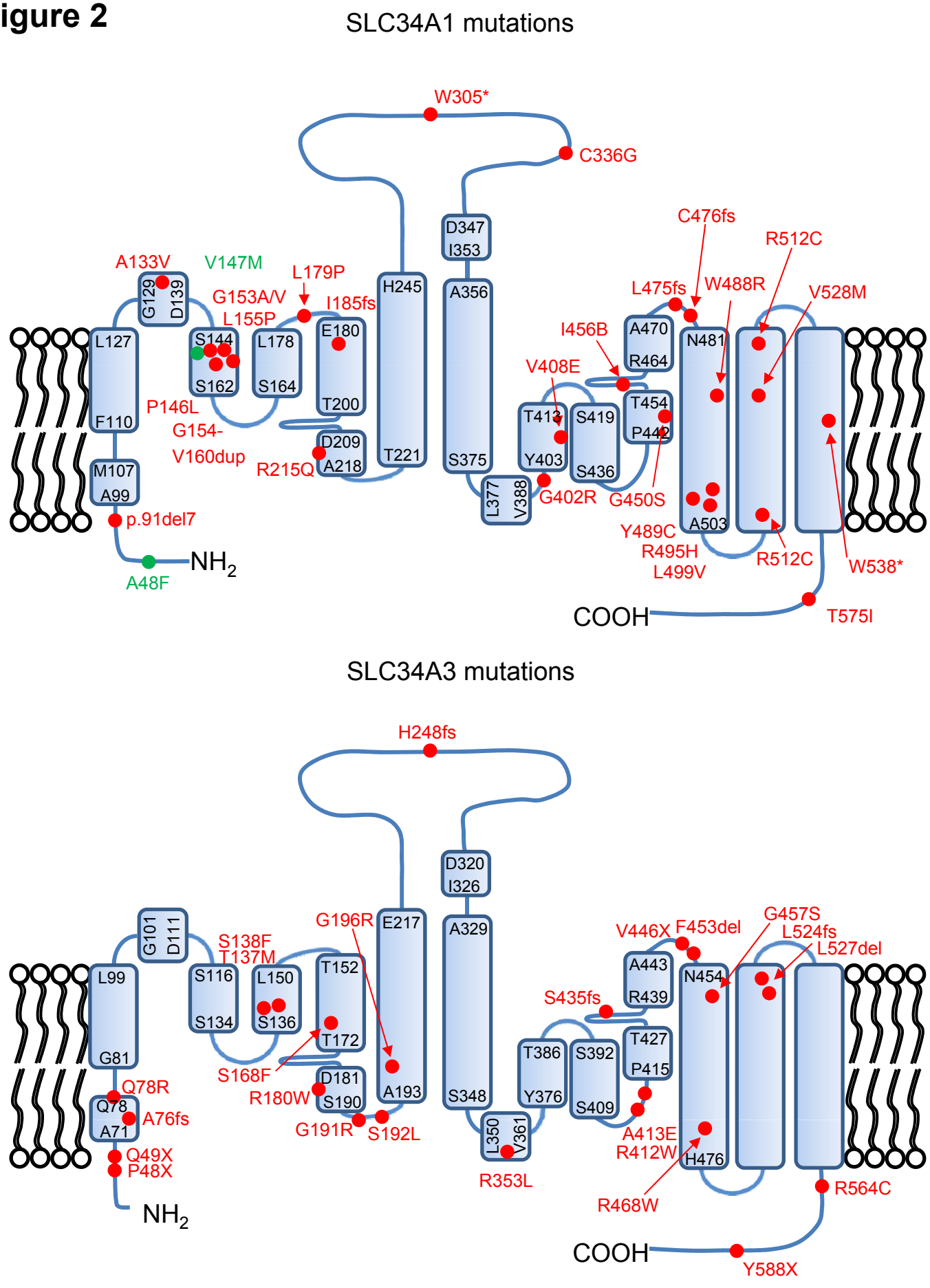

Urine
3Na+
HP04 2-
2Na+
HP04 2-
2Na+
H2P04 1-
NaPi-IIa
NaPi-IIc
Pit-2
HP04 2-
3Na+
2K+

Figure 2


SLC34A1 mutations
W305*
C336G
D347
I353
A356
S375
H245
T221
A133V
V147M
L179P
G153A/V
L155P
I185fs
G129
D139
L127
F110
S144
S162
L178
S164
E180
T200
D209
A218
P146L
G154-
V160dup
R215Q
M107
A99
p.91del7
A48F
NH2
L377
V388
G402R
V408E
T413
Y403
S419
S436
I456B
A470
R464
T454
P442
G450S
L475fs
C476fs
W488R
N481
R512C
V528M
A503
Y489C
R495H
L499V
R512C
W538*
T575I
COOH
SLC34A3 mutations
H248fs
D320
I326
A329
S348
E217
A193
G196R
G101
D111
S138F
T137M
S116
S134
L150
S136
T152
T172
S168F
D181
S190
R180W
G191R
S192L
L99
G81
Q78R
Q78
A71
A76fs
Q49X
P48X
NH2
L350
V361
R353L
T386
Y376
S392
S409
S435fs
A443
R439
T427
P415
A413E
R412W
R468W
V446X
F453del
N454
G457S
L524fs
L527del
H476
R564C
COOH
Y588X

Supplementary table 1

SLC34A1 Mutations

Position	Functionality	Disease	Refs
A48F	Dominant negative inhibition of transport ?	Nephrolithiasis and low bone density	[1]
91del7	Mild trafficking defect	Infantile idiopathic hypercalemia Nephrocalcinosis	[2-3]
A133V	Not tested	Nephrocalcinosis	[4-5]
P146L	Not tested	Nephrocalcinosis	[4]
V147M	Dominant negative inhibition of transport ?	Nephrolithiasis and low bone density	[1]
G153V G153A	Trafficking defect	Infantile idiopathic hypercalemia Nephrocalcinosis	[2, 4]
I154_V160dup	Small duplication	Fanconi-like syndrome	[6]
L155P	Trafficking defect	Infantile idiopathic hypercalemia Nephrocalcinosis	[2-3]
L179P	Not tested	Nephrolithiasis Hypercalciuria	[5]
I185fs	Frame shift	Infantile idiopathic hypercalemia Nephrocalcinosis	[2]
IVS6(+1)g>a	Not tested	Infantile idiopathic hypercalemia Nephrocalcinosis	[2, 5]
R215W	Trafficking defect	Infantile idiopathic hypercalemia Nephrocalcinosis	[2, 7]
W305*	Large truncation	Infantile idiopathic hypercalemia Nephrocalcinosis	[2]
IVS9(+3_6)del	Not tested	Infantile idiopathic hypercalemia Nephrocalcinosis	[2]
IVS9(+1)g>a	Not tested	Infantile idiopathic hypercalemia Nephrocalcinosis	[2]
C336G	Trafficking defect	Infantile idiopathic hypercalemia Nephrocalcinosis	[2]
G402R	Not tested	Nephrolithiasis Hypercalciuria	[5]
V408E	Trafficking defect	Infantile idiopathic hypercalemia Nephrocalcinosis	[2]
IVS12(+5)g>a	Not tested	Infantile idiopathic hypercalemia Nephrocalcinosis	[2]
G450S	Not tested	Nephrocalcinosis	[4]
I456B	Not tested	Nephrocalcinosis	[4]

I475 fs	Frame shift with trafficking defect	Infantile idiopathic hypercalemia Nephrocalcinosis	[2]
C476Sfs	Frame shift, not tested	Infantile idiopathic hypercalemia Nephrocalcinosis	[3]
W488R	Trafficking defect	Infantile idiopathic hypercalemia Nephrocalcinosis	[2]
Y489C	Not tested	Nephrolithiasis, low PTH, hypophosphatemia	[8]
R495H	Trafficking defect	Nephrocalcinosis, Hypophosphatemia	[9]
R512C	Not tested	Nephrolithiasis	[10]
W538*	Large truncation	Infantile idiopathic hypercalemia Nephrocalcinosis	[2]
T575I	Not tested	Nephrolithiasis Hypercalciuria	[5]

Supplementary table 2

SLC34A3 Mutations

Position	**Functionality**	**Disease**	**Refs**
Q49X	Large truncation	HHRH	[11]
c.175+1 G>A	Changes the first nt of the donor splice site of intron 3 (E59)	HHRH	[12]
c.228delC	Frame shift in A76 codon, introducing a early stop codon. Large truncation	HHRH	[13]
G78R	Not tested	HHRH	[14]
c.304+2T→C	Disrupts an essential residue at the donor splice site of intron 4	HHRH	[15]
c.367delC (counting contains the 5'UT)	Premature termination after residue p.P48	HHRH	[16]
T137M	Impaired expression and function	HHRH	[17]
S138F	Reduced membrane stability	HHRH	[13, 18]
g.1226G>A (IVS5 + 1G>A	Affects the splice donor site of intron 5	HHRH	[19]
S168F	Not tested	HHRH	[20]
R182W	Not tested	HHRH	[21]
g.1440–1469del	Deletion in intron 6: mRNA decay?	HHRH	[22]
G191R	Not tested	HHRH	[23]
S192L	Not tested	HHRH	[13, 15]
G196R	ER retention	HHRH	[13, 15, 18]

c.744delC	Frame shift after codon for H248, introducing an early stop codon	HHRH	[15]
c.757-1G>A	Affects the splice donor site of intron 7	HHRH	[24]
c.1046_47del	Frame-shift that introduces 242 unrelated amino acids in the C-terminus	HHRH	[22]
g.2259_2359del	Deletion of 101 bp within intron 9. Aberrant RNA splicing	HHRH	[13, 25]
R353L	Not tested	HHRH	[15]
g.2615–2699del	Deletion of 85 bp within intron 10. Aberrant RNA splicing	HHRH	[25]
W412R	Not tested	HHRH	[12]
A413E	Not tested	HHRH	[15]
c.1304delG	Frame shift in codon for S435, introducing a premature stop codon	HHRH	[26]
g.4225_50del	Deletion of the last 25 bp of intron 12 and the first bp of exon 13, which introduces a stop codon after V446. Abolished membrane expression	HHRH	[17]
F453del	Not tested	HHRH	[16]
G457S	Not tested	HHRH	[16]
R468W	ER retention		[13, 18]
c.1571_1880del	Truncation leading to frame shift in codon for L524, introducing a premature stop codon	HHRH	[22]
L527del	Not tested	HHRH	[13]
R564C	Reduced membrane stability	HHRH	[18]
Y588X	Not tested	HHRH	[22]

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